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(54) Title: KITS CONTAINING CYANOACRYLATE COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

(57) Abstract

Disclosed are kits of parts comprising a first container comprising a cyanoacrylate composition and a second container comprising a compatible antimicrobial agent and, in particular, a compatible iodine containing antimicrobial agent. Mixture of these compositions provide for *in situ* formation of an antimicrobial polymeric cyanoacrylate film on mammalian skin.

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KITS CONTAINING CYANOACRYLATE COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Patent Application Serial No. 08/962,869, filed November 3, 1997, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to kits of parts comprising in a first container a cyanoacrylate prepolymer composition and in a second container a compatible antimicrobial agent. The kit may additionally contain an applicator means for applying the composition to mammalian skin. These kits provide for compositions useful *in situ* formation of antimicrobial polymeric cyanoacrylate films on mammalian skin which films are useful as wound dressings, wound bandages, surgical incise drapes, and the like.

References

The following publications, patent applications and patents are cited in this application as superscript numbers:

[1] Hawkins, et al., *Surgical Adhesive Compositions*, U.S. Patent No. 3,591,676, issued July 6, 1971

[2] Halpern, et al., *Adhesive for Living Tissue*, U.S. Patent No. 3,667,472, issued June 6, 1972

[3] McIntire, et al., *Process for the Preparation of Poly(α-Cyanoacrylates)*, U.S. Patent No. 3,654,239, issued April 4, 1972

[4] Barley, et al., *Methods for Treating Non-Suturable Wounds by Use of Cyanoacrylate Adhesives*, International Patent Application Publication No. WO 93/25196, published December 23, 1993

[5] Barley, et al., *Methods for Treating Suturable Wounds by Use of Sutures and Cyanoacrylate Adhesives*, U.S. Patent No. 5,254,132, issued October 19, 1993

[6] Barley, et al., *Methods for Reducing Skin Irritation From Artificial Devices by Use of Cyanoacrylate Adhesives*, U.S. Patent No. 5,653,789, issued August 5, 1997

[7] Rabinowitz, et al., *Method of Surgically Bonding Tissue Together*, U.S. Patent No. 3,527,224, issued September 8, 1970

[8] Kronenthal, et al., *Surgical Adhesives*, U.S. Patent No. 3,995,641, issued December 7, 1976

[9] Davydov, et al., *Medical Adhesive*, U.S. Patent No. 4,035,334, issued July 12, 1977

[10] Waniczek, et al., *Stabilized Cyanoacrylate Adhesives Containing Bis-Trialkylsilyl Esters of Sulfuric Acid*, U.S. Patent No. 4,650,826, issued March 17, 1987

[11] Askill, et al., "*Methods for Draping Surgical Incision Sites*" U.S. Patent No. 5,730,994, issued March 24, 1998

[12] Greff, et al., *Cyanoacrylate Adhesive Compositions*, U.S. Patent No. 5,480,935, issued January 2, 1996

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[15] Osuna, et al., "*Comparison of an Antimicrobial Adhesive Drape and Povidone-Iodine Preoperative Skin Preparation in Dogs*", Veterinary Surgery, 21(6):458-462 (1992)

[16] O'Sullivan, et al., *High Viscosity Cyanoacrylate Adhesive Compositions, and Process for Their Preparation*, U.S. Patent No. 4,038,345, issued July 26, 1977

[17] Beller, et al., *Process for the Preparation of Iodine-Polyvinylpyrrolidone by Dry Mixing*, U.S. Patent No. 2,706,701, issued April 19, 1955

[18] Hosmer, *Process of Stabilizing Polyvinylpyrrolidone*, U.S. Patent No. 2,826,532, issued March 11, 1958

[19] Siggin, *Preparation of Iodine Polyvinylpyrrolidone Adducts*, U.S. Patent No. 2,900,305, issued August 18, 1958

[20] Joyner, et al., *Plasticized Monomeric Adhesive Compositions and Articles Prepared Therefrom*, U.S. Patent Nos. 2,784,127, issued March 5, 1957

[21] Columbus, et al., *Adhesive Cyanoacrylate Compositions with Reduced Adhesion to Skin*, U.S. Patent No. 4,444,933, issued April 24, 1984

[22] Leung, et al., *Biocompatible Monomer and Polymer Compositions*, U.S. Patent No. 5,328,687, issued July 12, 1994

[23] Byram, et al., *Use of Cyanoacrylate Adhesive Compositions to Inhibit Acute Radiation-Induced Skin Damage*, U.S. Patent No. 5,554,365, issued September 10, 1996.

[24] Leplyanin, "*Medical and Surgical Adhesive Composition and Process for Its Preparation*", International Application Publication No. WO 96/23532 published August 8, 1996

[25] Tighe, et al., "*Use of Cyanoacrylate Adhesives For Providing A Protective Barrier Film For The Skin*", U.S. Patent No. 5,580,565, issued on December 3, 1996.

[26] Cardarelli, et al., "*Film Forming Antimicrobial Material*", U.S. Patent No. 4,374,126, issued February 15, 1983

[27] Barnes, "*Biocidal Complex and Dressing Formed Therefrom*", U.S. Patent No. 5,051,256, issued September 24, 1991

[28] Dell, "*Film-Forming Composition Containing an Antimicrobial Agent and Methods*", U.S. Patent No. 4,542,012, issued September 17, 1985

[29] Brink, et al., "*Film-Forming Emulsion Containing Iodine and Methods of Use*", U.S. Patent No. 5,173,291, issued December 22, 1992

[30] Khan, et al., "*Preparation of a Skin Surface for a Surgical Procedure*", U.S. Patent No. 5,547,662, issued August 20, 1996

[31] Blum, et al., *In vitro Determination of the Antimicrobial Properties of Two Cyanoacrylate Preparations*, J. Dent. Res., 54(3):500-503 (1975)

[32] Greff et al., "*Cyanoacrylate Compositions Comprising an Antimicrobial Agent*", U.S. Patent No. 5,684,042, issued November 4, 1997

[33] Greff et al., "*Cyanoacrylate Compositions Comprising an Antimicrobial Agent*", U.S. Patent Application No. 08/912,681, filed August 18, 1997

[34] Mixon, U.S. Patent No. 5,069,907

[35] Greff et al., *Methods for Sterilizing Cyanoacrylate Compositions*, U.S. Patent Application Serial No. _____, filed October 15, 1998

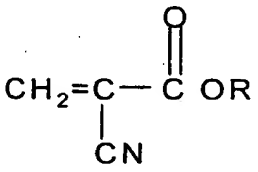
All of the above publications, patent applications and patents are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application or patent was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Cyanoacrylate esters have been disclosed for a variety of topical uses on mammalian skin including use as a replacement or adjunct for sutures or staples in closing the dermal layer of an incision after surgery.[1,2,5] Other disclosed topical uses include use as a hemostat[3], use in covering small non-suturable wounds on skin surfaces[4], use in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6] and use in inhibiting acute radiation-induced skin damage.[23] Still another topical use of cyanoacrylate esters is its use in the *in situ* formation

of a surgical incise drape.[11] In each case, when topically applied to mammalian skin, the cyanoacrylate rapidly polymerizes, typically within a minute, to form a coherent polymeric film which strongly adheres to the skin.

Cyanoacrylate esters suggested for such uses include the following structures:



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wherein R is an alkyl or other suitable substituent. Such cyanoacrylate esters are disclosed in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826.[1,2,7-10]

Cyanoacrylate ester compositions for topical skin application typically are formulated to contain both a plasticizer to enhance flexibility of the resulting polymeric film and a polymerization inhibitor to avoid premature polymerization of the composition. When employed topically on mammalian skin, Greff et al.[12] disclose that the cyanoacrylate composition preferably employs from about 50 to about 500 ppm sulfur dioxide as the polymerization inhibitor and from about 18-25 weight percent of a biocompatible plasticizer such as dioctyl phthalate.

Notwithstanding the beneficial properties associated with such cyanoacrylate ester compositions and their suitability for topical applications, these compositions do not possess a sufficient antimicrobial activity including activity against microbial spores[31] and, accordingly, cannot assure reductions in microbial populations on mammalian skin surface either under or adjacent to a polymeric cyanoacrylate film formed *in situ* on the skin.

Many of the uses of cyanoacrylate ester compositions enumerated above would, however, significantly benefit by additional antimicrobial property in the polymer film. For instance, covering small non-suturable wounds on skin surfaces with a polymeric cyanoacrylate film having antimicrobial activity would mitigate against possible wound infection. Likewise, when used as a surgical (incise) drape, such films would reduce microbial populations under and adjacent to the drape including those at the incision site and, accordingly, would reduce the risk of post-operative infection. Such is the basic premise of commercial surgical drapes containing an antimicrobial agent impregnated directly into the drape or an adhesive layer attached thereto where it was hoped that this agent would be released onto the skin surface to inhibit microbial growth.[13,14] Osuna, et al.[15] report, however, that when the antimicrobial agent is incorporated into the adhesive layer, the adhesive does not release sufficient amounts of the impregnated agent to be, by itself, antimicrobial.

As noted above, cyanoacrylate esters do not possess adequate antimicrobial activity and, accordingly, incorporation of antimicrobial properties into the cyanoacrylate polymeric film necessitates, of course, that an antimicrobially effective amount of an antimicrobial agent be incorporated into the prepolymeric cyanoacrylate composition and that sufficient amounts of this agent be released from the polymeric cyanoacrylate film onto the skin to achieve an antimicrobial effect. The incorporation of such an antimicrobial agent into the cyanoacrylate composition is problematic at best because several disparate criteria must be simultaneously met. First, the antimicrobial agent must be soluble or dispersible in the cyanoacrylate composition at the concentrations necessary to effect antimicrobial properties. Second, the antimicrobial agent employed must not cause premature polymerization of the cyanoacrylate ester composition. Third, the antimicrobial agent employed must not prevent *in situ* polymerization of the cyanoacrylate composition when applied to the skin. Fourth, the antimicrobial agent must be compatible with the intended use of the polymeric film by not

inhibiting formation of a flexible, durable film. Fifth, the impregnated antimicrobial agent must be released from the polymerized film *in situ* on the patient's skin in sufficient amounts to be antimicrobial.

Because of these disparate properties, many conventional antimicrobial agents are unsuitable for use in the prepolymeric compositions of this invention and typically the prior art has incorporated an antimicrobial agent into a solution or emulsion of the formed polymer or by direct mixing in the polymer melt (see, for example, Mixon[34]).

When an antimicrobial agent is incorporated into a solution/emulsion, placement of the solution/emulsion on the patient's skin followed by subsequent evaporation of the solvent results in a polymer film formed on the skin which film is permeated with the antimicrobial agent.[26,28-29] Since the polymer is preformed prior to application to the skin, these solutions/emulsions reduce the effective adherence of the polymer film to the skin and, accordingly, could lead to premature lifting or removal of the film from the skin. Moreover, the use of water and other solvents in the emulsion or solution can lead to slow drying times for the film with the concurrent difficulty in determining when or if the solvent has evaporated sufficiently to provide a polymer film on the patient's skin.[30] Organic solvents, on the other hand, forms noxious and potentially flammable fumes.

Kits containing an antimicrobial cyanoacrylate composition and an applicator means have been described in Greff et al., U.S. Patent Application No. 08/912,681[33]. Because the cyanoacrylate composition and the antimicrobial agent are premixed in the kit, such a mixture may have a reduced shelf-life because of the premature polymerization of the cyanoacrylate ester over time (e.g., months). Furthermore, certain antimicrobial agents cannot be formulated in such kits because they cause premature polymerization of the cyanoacrylate ester. Finally, sterilization of the cyanoacrylate/antimicrobial mixture, if desired, may result in

premature polymerization of the composition in the container and the various components of the composition may be sterilized. The method of sterilization may be the method set forth in Askill et al.[35], U.S. Serial No. _____, filed October 15, 1998, which is incorporated by reference

In view of the clear benefits associated with the incorporation of an antimicrobial agent into the monomeric cyanoacrylate composition prior to application of the cyanoacrylate composition onto mammalian skin, there is a need for a kit which comprises a cyanoacrylate composition in a first container and an antimicrobial agent in a second container such that the composition and agent can be mixed immediately prior to use and the resulting composition applied to mammalian skin.

SUMMARY OF THE INVENTION

This invention is directed to kits of parts comprising a polymerizable cyanoacrylate ester composition in a first container and an antimicrobially effective amount of a compatible antimicrobial agent in a second container. When the contents of these containers are mixed, a polymerizable antimicrobial cyanoacrylate composition is provided which permits *in situ* formation of an antimicrobial polymeric cyanoacrylate film on mammalian skin. The specific antimicrobial agent employed is compatible with the cyanoacrylate composition insofar as the antimicrobial agent neither causes premature polymerization nor prevents polymerization of the monomer. Rather a flexible and durable polymeric film is formed *in situ* on mammalian skin by the mixture of these two compositions and application of the mixture onto the skin. Moreover, *in vitro* assays evidence that the antimicrobial agent is released from the polymeric film in antimicrobially effective amounts thereby imparting antimicrobial properties to the polymeric film.

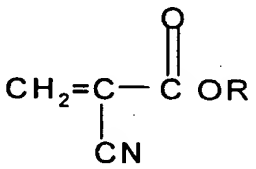
Accordingly, in one of its kit aspects, this invention is directed to kit of parts which comprises:

(a) a first container comprising therein a polymerizable cyanoacrylate ester; and

(b) a second container comprising therein an antimicrobially effective amount of a compatible antimicrobial agent.

Optionally, multiple containers can be used to store separate antimicrobial components if a mixture of more than one antimicrobial agent is employed.

Preferably, the polymerizable cyanoacrylate ester is a polymerizable monomer or reactive oligomer of a cyanoacrylate ester. Such monomers and reactive oligomers are sometimes referred to herein simply as "prepolymers" and, in monomeric form, are preferably represented by formula I:



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wherein R is selected from the group consisting of:

alkyl of 1 to 10 carbon atoms,

alkenyl of 2 to 10 carbon atoms,

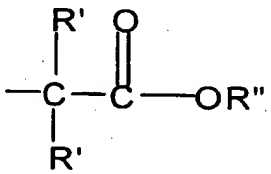
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of the formula:



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wherein each R′ is independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

More preferably, in the cyanoacrylate esters of formula I, R is alkyl of from 2 to 10 carbon atoms and still more preferably an alkyl of from 4 to 10 carbon atoms. Even more preferably, R is butyl, pentyl, octyl, decyl or mixtures thereof and most preferably R is *n*-butyl.

The kit of parts preferably further comprises an effective amount of polymerization inhibitors and a biocompatible plasticizer. Suitable polymerization inhibitors are well known in the art and include 4-methoxyphenol (50 to 1000 ppm based on weight of composition absent any antimicrobial agent) and sulfur dioxide (50 to 1000 ppm based on weight of composition absent any antimicrobial agent). Other preferred polymerization inhibitors include acid inhibitors, e.g., glacial acetic acid and other organic acids, and free radical inhibitors (e.g. hydroquinones, hindered phenols) and the like which can be used alone or in combination with 4-methoxyphenol and/or SO_2.

The preferred biocompatible plasticizer is dioctyl phthalate or C_2-C_4-acyl tri-n-alkyl (C_1-C_6) citrates. The plasticizer is preferably employed at from about 18 to 25 weight percent based on the total weight of the composition absent the antimicrobial agent.

In one embodiment, the first container of the kit which comprises the cyanoacrylate composition, further comprises the polymerization inhibitor and the biocompatible plasticizer.

In another embodiment, the kit of parts further comprises an applicator means for applying the composition onto mammalian skin which, preferably, is an integral part of one of the containers employed in the kit.

DESCRIPTION OF THE DRAWINGS

FIG.s 1A and 1B are a top plan view of a kit of parts comprising a first container having solid PVP-I_2 and a second container containing a polymerizable cyanoacrylate composition, which containers can be mixed at the appropriate time to obtain a polymerizable antimicrobial cyanoacrylate composition.

FIG.s 2A, 2B are a top plan view of a another kit of parts. FIG 2A illustrates a container comprising a first and second compartment containing a polymerizable cyanoacrylate composition and tetracycline hydrochloride separated by a temporary barrier. FIG 2B illustrates the second container.

FIG.s 3A, 3B and 3C illustrate another kit of parts. FIG 3A is a perspective view of the kit. FIG. 3B is a cross-section through the kit with the temporary seal intact. FIG. 3C is a cross-section through the kit after the temporary seal is broken.

FIG.s 4A and 4B illustrate another embodiment of the kit of parts. FIG 4A is a perspective view of the kit and FIG 4B is a cross-sectional of the kit with the temporary seal intact.

FIG.s 5A and 5B illustrate another kit of parts. FIG. 5A is a cross-section of the kit. FIG.5B is a perspective view of the kit.

FIGs. 6A and 6B illustrate another kit of parts comprising a first frangible container enclosed within a second container. FIG 6A is a cross-section of the kit with the first container intact. FIG. 6B is a cross-section of the kit after the second container is bent, breaking the first container and releasing its contents into the second container.

FIGs. 7A, 7B and 7C illustrate another embodiment of the kit of parts.

FIG.8 is a cross-section of another kit of parts.

FIG. 9 is an exploded cross-sectional view of another kit of parts.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed, in part, to a kit of parts comprising therein a first container comprising a cyanoacrylate composition and a second container comprising therein an antimicrobially effective amount of a compatible antimicrobial agent. However, prior to discussing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, the following terms have the following meanings:

The term "cyanoacrylate ester compositions" or "cyanoacrylate compositions" refers to polymerizable formulations comprising polymerizable cyanoacrylate ester monomers and/or oligomers which, in their monomeric form, are preferably compounds represented by formula I as described above. Such compounds have been described in Greff et al. [32,33] which are incorporated by reference herein.

Preferably, in formula I, R is an alkyl group of from 2 to 10 carbon atoms and more preferably an alkyl group of from 4 to 10 carbon atoms including, by way of example, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl, *iso*-hexyl, 2-ethylhexyl, *n*-heptyl, *n*-octyl, nonyl, and decyl. More preferably, R is butyl, pentyl, octyl or decyl and most preferably, R is *n*-butyl. Mixtures of such compounds can also be employed.

Polymerizable cyanoacrylate esters are known in the art and are described in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826[1,2,7-10] the disclosures of each are incorporated herein by reference in their entirety.

A particularly preferred cyanoacrylate ester for use in the invention is *n*-butyl-2-cyanoacrylate.

The polymerizable cyanoacrylate ester compositions described herein rapidly polymerize in the presence of water vapor or tissue protein, and the cyanoacrylate bonds human skin tissue without causing histotoxicity or cytotoxicity.

Such polymerizable cyanoacrylate esters are sometimes referred to herein as prepolymers and compositions comprising such esters are sometimes referred to herein as prepolymer compositions.

The term "antimicrobial agent" refers to agents which destroy microbes (i.e., bacteria, fungi, viruses, parasites and microbial spores) thereby preventing their development and pathogenic action.

The term "compatible antimicrobial agent" means an antimicrobial agent which is compatible with the cyanoacrylate composition insofar as the antimicrobial agent causes neither premature polymerization nor prevents polymerization of the polymerizable cyanoacrylate composition *in situ*.

The term "premature polymerization" means that the mixture of the cyanoacrylate and antimicrobial agent polymerizes so quickly in the container that the mixture cannot be effectively applied to mammalian skin prior to polymerization. Preferably polymerization of the cyanoacrylate composition in the container does not occur within about 30 minutes of mixing of the antimicrobial agent with the cyanoacrylate composition. More preferably, the antimicrobial agent does not cause polymerization in the container of the cyanoacrylate composition within about 15 minutes of mixing.

Suitable compatible antimicrobial agents include the antimicrobial complexes of iodine molecules with a biocompatible polymer, hexachlorophene, tetracycline hydrochloride and the like.

Such antimicrobial complexes of iodine molecules with a biocompatible polymer preferably include polyvinylpyrrolidone polymers which are also referred to under the common name of Povidone or PVP (commercially available from BASF, Mt. Olive, New Jersey, USA), copolymers of vinylpyrrolidone and vinyl acetate, copolymers of vinylpyrrolidone and vinyl acetate cross-linked with polyisocyanates, copolymers of vinylpyrrolidone and vinyl functionalities, polymers of pyrrolidone[27] and the like. Preferably, the iodine containing polymer is Povidone Iodine which is commercially available from a number of sources.

The term "a biocompatible polymer" refers to polymers which, as iodine complexes (adducts), are compatible with *in vivo* applications of cyanoacrylate ester compositions onto mammalian skin including human skin. Representative polymers include polyvinylpyrrolidone, copolymers comprising polyvinylpyrrolidone which is optionally crosslinked, and the like. Suitable copolymers include copolymers of polyvinylpyrrolidone and vinyl acetate or other vinyl compounds which copolymers are optionally crosslinked with a polyisocyanate. The molecular weight of these polymers is not critical with number average molecular weights ranging from about 10,000 to about 1,000,000 and preferably from 30,000 to 300,000 being preferred.

The term "a complex of iodine molecules with a biocompatible polymer" refers to an antimicrobial complex formed by the addition of iodine (I_2) to the biocompatible polymer. Such complexes are well known in the art and the resulting complex typically comprises both available iodine and iodine anions. These complexes, on contact with mammalian skin, are antimicrobial apparently by providing for a source of antimicrobial iodine. In any event, such complexes are employed only as starting materials herein and, by themselves, do not form a part of this invention.

These complexes are sometimes referred to herein simply by the term "iodine/polymer complexes". Elemental (solid) iodine, on the other hand, is incompatible with cyanoacrylate compositions because the addition of elemental iodine renders such compositions non-polymerizable on mammalian skin. Accordingly, complexation of the iodine with the biocompatible polymer is apparently essential for compatibility with the cyanoacrylate composition.

A preferred iodine/polymer complex for use in the compositions of this invention is a polyvinylpyrrolidone iodine complex which is described in, for example, U.S. Patent Nos. 2,706,701, 2,826,532 and 2,900,305[17-19] as well as at pp.

1106-1107 of the Tenth Edition of the Merck Index, Published by Merck & Co., Rahway, N.J., USA (1983) the disclosures of which are incorporated herein by reference in their entirety. This complex is commercially available under the name "povidone-iodine" from BASF, Mt. Olive, New Jersey, USA.

The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in the cyanoacrylate composition, which increases the flexibility of the resulting polymer film coating on the skin surface, and which, in the amounts employed, is compatible with the skin as measured by the lack of moderate to severe skin irritation. Suitable plasticizers are well known in the art and include those disclosed in U.S. Patent Nos. 2,784,127[20] and 4,444,933[21] the disclosures of both of which are incorporated herein by reference in their entirety. Specific plasticizers include, by way of example only, acetyl tri-*n*-butyl citrate (preferably ~20 weight percent or less), acetyl trihexyl citrate (preferably ~20 weight percent or less) butyl benzyl phthalate, dibutyl phthalate, dioctylphthalate, *n*-butyryl tri-*n*-hexyl citrate, diethylene glycol dibenzoate (preferably ~20 weight percent or less) and the like. The particular biocompatible plasticizer employed is not critical and preferred plasticizers include dioctylphthalate and C_2-C_4-acyl tri-n-alkyl (C_1-C_6) citrates.

The term "polymerization inhibitor" refers to any material which is soluble or dispersible in the cyanoacrylate composition and which, in the amounts employed, inhibits the premature polymerization of the composition and is compatible with the skin. Conventional acid inhibitors of cyanoacrylate esters including materials such as sulfur dioxide, glacial acetic acid, organic acids, and the like. The polymerization inhibitor is typically employed in amounts effective to inhibit polymerization until application onto the mammalian skin. Suitable polymerization inhibitors are well known in the art and include sulfur dioxide. Other preferred polymerization inhibitors include free radical inhibitors (e.g.

hydroquinones, hindered phenols) and the like which can be used in combination with acid inhibitors such as SO_2. Preferably, the polymerization inhibitor is employed at from about 50 to about 1000 ppm based on the total weight of the composition absent any antimicrobial agent and more preferably from about 100 to 500 ppm.

Compositions

This invention is based on the novel and unexpected discovery that the antimicrobial agents described herein are compatible with cyanoacrylate esters forming a polymerizable composition which, upon polymerization, provides for an antimicrobial cyanoacrylate polymeric film. Compatibility is assessed by the fact that these agents are dispersible in the cyanoacrylate ester composition at antimicrobially effective concentrations and when so employed, do not cause premature polymerization of the cyanoacrylate ester composition and do not prevent effective polymerization of the cyanoacrylate ester composition when applied to mammalian skin. Moreover, the polymerizable cyanoacrylate ester composition comprising such complexes forms a flexible, durable polymeric film having the complex incorporated therein which complex is released from the film in sufficient amounts to provide antimicrobial properties to the film.

The specific amount of antimicrobial agent required to effect antimicrobial properties in the resulting polymeric film can be readily measured by conventional *in vitro* assays measuring zones of microbial growth inhibition around the film. Zones of inhibition of at least 1 millimeter and preferably 3 millimeters from the edge of the film when tested in the manner of Example 2 below evidence that the polymeric film is antimicrobial. Assessing the amount of antimicrobial agent required in the polymeric film to effect such a zone of inhibition is well within the skill of the art.

When tetracycline is employed as the antimicrobial agent, it is preferably employed as the hydrochloride salt. Such a preference reflects the rapid polymerization of the cyanoacrylate composition when tetracycline hydrate is employed.

When an iodine/polymer complex is employed as the antimicrobial agent, it is preferably added as the commercially available solid composition rather than as the commercially available aqueous or ethanolic solution insofar as the solution can cause premature polymerization of the cyanoacrylate ester which is apparently due to solvent's effects. Preferably, the iodine/polymer complex added is micronized , i.e. each particle is sized to be about 10 microns. Such iodine/polymer complexes are commercially available or can be made by conventional means using a ball mill. Upon addition of the solid iodine/polymer complex to the cyanoacrylate prepolymer composition, the resulting system is thoroughly mixed to obtain a homogeneous suspension.

The amount of antimicrobial agent added to the cyanoacrylate composition is a sufficient amount such that the resulting polymeric film is antimicrobial. Preferably, from about 1 to about 40 weight percent of the antimicrobial agent is employed based on the total weight of the composition. More preferably, from about 1 to 10 weight percent of tetracycline hydrochloride is employed; from 1 to 15 weight percent of hexachlorophene is employed; and from about 1 to 40 weight percent of the iodine/polymer complex is employed. When the size of the iodine/polymer particles is approximately 30 mesh the amount employed is preferably from about 10 to 30 weight percent. When the size of the iodine/polymer particles is micronized (e.g., approximately 10 μm) the amount employed is preferably from about 1 to 20 weight percent and more preferably from about 3 to 10 weight percent.

The composition of the antimicrobial agent and the cyanoacrylate ester can be formulated to a specific viscosity to meet disparate demands for the intended application of the composition. For example, relatively low viscosities are often preferred where application is to be made to a large surface area (e.g., abdominal surfaces). This preference results from the fact that these forms are less viscous and, accordingly, will permit more facile large surface area application of a thin film. Contrarily, where application is to be made to a specific position on the skin (e.g., elbow surfaces, knee surfaces and the like), higher viscosity compositions, including those containing thixotropic materials, are preferred to prevent "running" of the compositions to unintended locations.

Accordingly, these compositions have a viscosity of from about 2 to 50,000 centipoise at 20°C. For low viscosity applications, viscosity ranges of from about 2 to 1,500 centipoise at 20°C are preferred. More preferably, the cyanoacrylate ester employed in the composition is almost entirely in monomeric form and the composition has a viscosity of from about 5 to about 500 centipoise at 20°C.

A thickening agent is optionally employed to increase the viscosity of the composition which thickening agent is any biocompatible material which increases the viscosity of the composition. Suitable thickening agents include, by way of example, polymethyl methacrylate (PMMA) or other preformed polymers soluble or dispersible in the composition, a suspending agent such as fumed silica and the like, with PMMA being preferred. Fumed silica is particularly useful in producing a gel for topical application having a viscosity of from about 1500 to 50,000. Suitable thickening agents for the cyanoacrylate compositions described herein also include a polymer of the alkyl cyanoacrylate as disclosed in U.S. Patent Nos. 3,654,239[3] and 4,038,345[16] both of which are incorporated herein by reference in their entirety.

Thickening agents are deemed to be biocompatible if they are soluble or dispersible in the composition and are compatible with the skin as measured by the lack of moderate to severe skin irritation.

The cyanoacrylate composition preferably includes a biocompatible plasticizer and such plasticizers are preferably included from about 10 to 30 weight percent and more preferably from about 18 to 25 weight percent based on the weight of the composition absent the antimicrobial agent. A particularly preferred biocompatible plasticizer for use in the compositions described herein is dioctylphthalate and C_2-C_4-acyl tri-n-alkyl (C_1-C_6) citrates.

The cyanoacrylate ester compositions may additionally contain one or more optional additives such as colorants, perfumes, rubber modifiers, modifying agents, etc. In practice, each of these optional additives should be both miscible and compatible with the cyanoacrylate composition and the resulting polymer. Compatible additives are those that do not prevent the use of the cyanoacrylates in the manner described herein.

In general, colorants are added so that the polymer layer formed on the skin will contain a discrete and discernable color. Perfumes are added to provide a pleasant smell to the formulation. Rubber modifiers are added to further enhance the flexibility of the resulting polymer layer. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

Additionally, the cyanoacrylate composition can optionally comprise a formaldehyde scavenger compound such as those described by Leung, et al.[22] The use of such scavengers has been suggested as enhancing internal *in vivo* applications of cyanoacrylates.

Still further, it is contemplated that the cyanoacrylate composition can optionally comprise an acrylic monomer that will act as a polymeric plasticizer when it copolymerizes with the cyanoacrylate composition.[24]

Utility

The methods described herein are useful in forming *in situ* an antimicrobial polymeric film on the skin surface of a mammalian patient. Such mammalian patients preferably include humans as well as, for example, domestic animals such as horses, cows, dogs, sheep, cats, etc.

The polymeric film finds particular utility in inhibiting microbial contamination thereunder and in the areas immediately adjacent thereto. Accordingly, such polymeric films can be used to topically cover small non-suturable wounds on skin surfaces which wounds do not penetrate through the dermal layer of the skin as in the manner described in Barley, et al.[4] When so employed, the antimicrobial cyanoacrylate composition is applied over the small non-suturable wound. Upon polymerization, an antimicrobial polymeric film is formed over the wound which provides for antimicrobial properties at the wound surface while also preventing exogenous contaminants from entering the wound.

Additionally, the polymeric films formed from the antimicrobial cyanoacrylate compositions described herein can also be used in the *in situ* formation of a surgical incise drape in the manner described by Askill, et al.[11]. When so employed, the *in situ* formed film strongly adheres to the mammalian skin surface to provide for a surgical incise drape which does not lift during surgery and has antimicrobial properties.

When used as either a small wound covering or as a surgical incise drape, the antimicrobial polymeric film will only adhere to the skin for a period of about 1-4 days after which time it sloughs off. This occurs because the cyanoacrylate

polymer adheres only to the uppermost portion of the epidermal layer which is continuously in the process of being sloughed off and replaced by the underlying cells. Accordingly, the antimicrobial cyanoacrylate film need not be removed after *in situ* formation. However, if removal of the polymeric film is required, such can be accomplished with a material such as acetone (nail polish remover).

Other utilities for the compositions of this invention include their use to form polymeric hemostatic films[3], use as protective barriers through which needle punctures or catheter placement occurs, use to form polymeric films in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6], use in forming polymeric films in inhibiting acute radiation-induced skin damage[23], use in treating incontinence and areas adjacent to wounds to stomas[25] and use in wound closure materials as an replacement or adjunct to sutures.

Kits

In view of the many different uses for topical application onto mammalian skin, this invention encompasses a kit of parts useful for applying the antimicrobial cyanoacrylate compositions described herein onto mammalian skin. The multi-component system can be used to store the antimicrobial agent in one component of the container and the polymerizable cyanoacrylate composition in the other component. At the appropriate time, the components can be mixed to provide for an antimicrobial, polymerizable cyanoacrylate composition.

In particular, such a kit of parts comprises (a) a first container comprising a polymerizable cyanoacrylate composition and (b) a second container comprising a compatible antimicrobial agent as described above. The kit may further comprise an applicator means for applying onto mammalian skin the antimicrobial polymerizable cyanoacrylate composition obtained by mixing the contents of the two containers. In one embodiment, the applicator means is attached to one of the

containers. In another embodiment, the applicator means forms a discrete part of the kit.

In one embodiment, the containers are combined into a single article of manufacture having a barrier between the containers/compartments. This barrier can either be removed or destroyed allowing mixing of the compositions in each of the compartments at the appropriate time. Such barriers include frangible or crushable barriers.

In another embodiment, the first and second containers are separate articles designed to mate with each other. For example, the cyanoacrylate prepolymer composition could be stored in an amber vial sealed with a screw cap and the antimicrobial agent is stored in a second vial which includes a screw mechanism which mates with the screw mechanism on the top of the cyanoacrylate vial. When mixing of the cyanoacrylate prepolymer composition with the antimicrobial agent is intended, the caps are removed from the cyanoacrylate vial and the antimicrobial vial and the vials are attached and the components mixed.

The first container or compartment comprises any compatible material which stores the cyanoacrylate composition without degradation of the container/compartment or prematurely polymerizing the cyanoacrylate prepolymer. Such materials include, by way of example, inorganic materials such as Type 1 glass (including amber colored glass), ceramics, metals (e.g., aluminum, tin and tin coated tubes), etc. and organic materials such as inert polymers including polyolefins (e.g., high density polyethylene), fluorinated polyolefins, and the like. Examples of suitable containers include those recited in Bolduc, U.S. Patent No. 5,154,320, which is incorporated herein by reference in it entirety.

The second or further container/compartment contains the antimicrobial and can optionally include glass beads or other similar materials to facilitate

mixing of the contents of the two containers when mixing is desired. The container/compartment comprising the antimicrobial agent is prepared from materials which are compatible with the antimicrobial agent or mixture of agents employed therein.

Suitable applicator means include brushes, rollers, aerosols, swabs, foams (e.g., polyethylene foam), packed fibers and the like. A particularly preferred applicator is described in U.S. Patent No. 4,183,684.

Dispensing units of the general type with which this application is concerned are known in the art. Pertinent in this respect are the dispensing devices described in U.S. Patent Nos. 4,183,684; 5,409,141; 5,474,209; 4,648,532 and 5,466,220 each of which is incorporated by reference herein.

In one embodiment, one of the containers (e.g. the first container or the second container) and the applicator means are combined into a single article such as a brush affixed to the terminal portion of the container wherein means are employed to prevent premature release of the cyanoacrylate prepolymeric composition. For example, the brush may be overlayed with a removable impermeable barrier. When application of the cyanoacrylate prepolymer composition is intended, the barrier is simply removed.

FIG.s 1A, 1B, 2A, 2B, 3A, 3B, 3C, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 7C and 8 illustrate various types of containers in which the polymerizable cyanoacrylate composition is separated from the antimicrobial agent prior to mixing.

FIG. 1A illustrates a first container **2** comprising a terminal applicator means **4** and container element **6** which, in this embodiment, comprises glass beads **14** and the requisite amount of solid PVP-I_2 **16**. First container **2** has mating

threads **18** for mating with cap **8** during storage. Cap **8** is mated to first container **2** during storage in order to retain both the glass beads **14** and PVP-I_2 **16** in container element **6**.

FIG. 1B illustrates the second container **10** comprising mating threads **11** which mate with the reciprocal mating threads **18** when the first and second containers **2** and **10** are joined. Container **10** comprises a temporary seal means **12** which seals the polymerizable cyanoacrylate composition **13** within container **10** until mixing with the PVP-I_2 **16** is desired. Suitable temporary seal means include puncturable plastics, glasses, foils, films, etc. as well as peelable plastics, foils, films, etc. In one embodiment, mating means **18** can include a puncturing element (not shown) which can puncture the temporary seal means **12**.

When mixing of the first and second containers **2** and **10** is desired, cap **8** is removed from first container **2** and temporary seal means **12** are removed or punctured from second container **10** and the two containers mated via complementary mating threads **18** and **11**. Upon mating, the contents are mixed to provide for a homogenous suspension of the PVP-I_2 **16** in the cyanoacrylate composition **13** which can be applied to mammalian skin (not shown) via applicator means **4**.

FIG.s 2A and 2B illustrate an alternative means of forming a suitable kit of parts. Specifically, in FIG. 2A, container **20** comprises two compartments **21** and **23** separated by temporary barrier means **26**. Compartment **21** comprises glass beads **14** and the requisite amount of tetracycline hydrochloride **19**. Compartment **23** comprises polymerizable cyanoacrylate composition **13** as well as mating means **24** and temporary seal means **22**. Suitable temporary seal means **22** include, by way of example, puncturable plastics, glasses, foils (aluminum, tin, etc.), films, etc. as well as peelable plastics, foils, films, etc.

FIG. 2B illustrates the second container **28** comprising mating threads **34** which mate with the reciprocal mating threads **24** when the first and second containers **20** and **28** are joined. Container **28** comprises a removable cap **27** which covers applicator tip **25** until application of the mixed composition. In the embodiment illustrated, mating means **29** includes a puncturing element **17** which punctures the temporary seal means **22** during mating.

When mixing of the contents of the first and second compartments **21** and **23** is desired, removal of barrier means **26** in an appropriate manner (e.g., shaking, squeezing, heating, crushing, etc.) allows for mixing of the components. For example, vigorous shaking of the contents permit the glass beads to break barrier means **26**. Mixing in this manner can occur either prior to or after mating of the first and second containers, **20** and **28**.

Mating is achieved in the manner set forth above.

Alternatively, in FIG.s 2A and 2B, the tetracycline hydrochloride is stored in second container **28**.

FIG.s 3A, 3B and 3C illustrate an alternative means of forming a suitable kit of parts in which the containers are combined into a single article of manufacture having a barrier between the containers or compartments. In FIG. 3A, container **30** comprises two containers **31** and **32**, wherein container **32** is slidably engaged within container **31** and a locking means **40**. FIG. 3B illustrates that container **32** is closed at one end by a first temporary seal means **33** and is separated into two compartments **36** and **37** by a second temporary seal means **34**. Container **31** comprises a suitable puncturing element **38** and an applicator means **41**. Compartment **36** comprises polymerizable cyanoacrylate composition **35**. Compartment **37** comprises the requisite amount of antimicrobial **39**. Suitable

temporary seal means **33** and **34** include, by way of example, puncturable plastics, glasses, foils (aluminum, tin, etc.), films, etc.

When mixing of the polymerizable cyanoacrylate composition **35** and the antimicrobial **39** is desired, the removable locking means **40** is removed and container **32** is slidably moved into container **31** such that both the first and second temporary seal means **33** and **34** are punctured by the puncturing element **38**. See FIG. 3C. Upon puncturing, the contents are mixed to provide for a homogeneous suspension of the antimicrobial **39** in the cyanoacrylate composition **35** which can then be applied to mammalian skin via the applicator means **41**.

FIG.s 4A, and 4B illustrate a further embodiment of the container of FIG.s 3A, 3B, and 3C wherein the applicator means **41** is angled.

FIG.s 5A and 5B illustrate a further embodiment of the container of Figs. 3A, 3B and 3C wherein the locking means **40** comprises a compressible ring interposed between containers **31** and **32**, such that upon compression, both the first and second temporary seal means **33** and **34** are punctured by the puncturing element **38**.

The applicator means can be applied to either of the containers.

FIG.s 6A and 6B illustrate a further container **50** comprising a first breakable container **51** located entirely within a second container **52**. The first breakable container **51** contains the polymerizable cyanoacrylate composition **53**. The second compartment comprises an applicator means **54**, a flexible region **55** and the antimicrobial **56**. The first breakable container **51** may, for example, be a thin wall glass ampoule

When mixing of the polymerizable cyanoacrylate composition **53** and the antimicrobial **56** is desired, the second container **52** is bent at the flexible region **55**, thereby breaking the first container **51**. The cyanoacrylate composition **53** is released from the first compartment **51** into the second compartment **52** where it mixes with the antimicrobial **56** which can then be applied to mammalian skin via the applicator means **54**. The flexible region may include, for example, a stress riser to aid in breaking the first container **51**.

FIGs. 7A, 7B and 7C are perspective views of other embodiments of kit of parts, in which the second container **52** further comprises hollow flanges or fins **60** with are integral to the container and which are engaged with the applicator means **54**. Such fins or flanges **60** serve to transfer the mixture of the cyanoacrylate composition and antimicrobial to the applicator means **54**.

FIG. 8 is another embodiment of a kit of parts, in which the second container is formed from a tube which is sealed flat at one end with the applicator means **54** located at the opposite end.

FIG. 9 is an exploded cross-sectional view of another kit of parts comprising an outer first container **70**, a second flexible container **71** and an applicator means **72**. The second flexible container **71** comprises a first compartment **73** containing the cyanoacrylate composition **74** and a second compartment **75** containing the antimicrobial powder **76** with a frangible seal **77** separating the first and second compartments. The second compartment **75** is open at one end, which end is placed in the applicator means **72**. When mixing of the cyanoacrylate and the antimicrobial is desired, the frangible seal **77** is broken and the cyanoacrylate composition and the antimicrobial are mixed and applied to the mammalian skin with the applicator means **72**.

Multiple component systems can also be used (e.g., a three component system comprising two components each containing a separate antimicrobial agent each stored in separate compartments segregated from each other until time of use as well as a third component storing the cyanoacrylate composition). In another embodiment, the cyanoacrylate polymer is stored in one container, the antimicrobial agent is stored in another container and the biocompatible plasticizer is stored in a third container.

The following examples illustrate certain embodiments of the invention but are not meant to limit the scope of the claims in any way.

EXAMPLE

In the example below, all temperatures are in degrees celsius (unless otherwise indicated) and all percents are weight percent (also unless otherwise indicated) except for percent inhibition which is true mathematical percentage. Additionally, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

CFU	=	colony forming units
conc.	=	concentration
flex.	=	flexibility
dur.	=	durability
ml	=	milliliters
mm	=	millimeters
ppm	=	parts per million
PVP-I_2	=	polyvinylpyrrolidone iodine complex
SAB-DEX	=	Sabouraud Dextrose
TSA	=	trypticase soy agar

EXAMPLE 1

The following example examines the compatibility of different antimicrobial agents in cyanoacrylate compositions. In particular, the composition employed monomeric *n*-butyl cyanoacrylate containing 100 ppm sulfur dioxide and

20 weight percent of dioctyl phthalate absent the antimicrobial agent. In each case, either 5 weight percent, 10 weight percent or 20 weight percent of the antimicrobial agent, based on the total weight of the composition, was added thereto and the properties of the resulting composition measured. The antimicrobial agents tested were elemental iodine, solid polyvinylpyrrolidone iodine, a 30% aqueous solution of polyvinylpyrrolidone iodine, silver nitrate, merbromin, tetracycline hydrate, and erythromycin (each of these antimicrobial agents were obtained from commercial sources).

The evaluation included assessing whether the antimicrobial agent was soluble or suspendable in the composition; whether the resulting composition cured upon contact with skin; whether curing provided for a polymeric film *in situ* on the skin; whether the polymeric film was flexible and durable. Solubility and suspendability were determined by conventional standards. The ability of the resulting composition to cure *in situ* upon application to skin was measured by applying the cyanoacrylate composition onto the upper arm of a male human subject and determining whether polymerization proceeded (up to 5 minutes) and, if so, the time required for polymerization. Film forming capabilities on the skin were assessed by visual evaluation. Durability was assessed by determining whether the film was retained on the skin surface for at least 24 hours and flexibility was measured by the ability of the film to be retained on the skin without cracking or peeling for at least 24 hours. The results of this evaluation are summarized in Table I below:

TABLE I

Antimicrobial Agent	Conc.	Soluble	Curable	Film Formed	Flex.	Dur.
elemental iodine (I_2)	~20%	partially	No (when tested for 5 minutes)	--	--	--

Antimicrobial Agent	Conc.	Soluble	Curable	Film Formed	Flex.	Dur.
PVP-I_2 solid	10%	no suspension[2]	Yes (30 seconds)	Yes	Yes	Yes
PVP-I_2 solution	10%	no, gelled[1]	--	--	--	--
Silver nitrate	5%	no, gelled[1]	--	--	--	--
Merbromin	5%	no, gelled[1]	--	--	--	--
tetracycline hydrate	5%	no, gelled[1]	--	--	--	--
Erythromycin	5%	no, gelled[1]	--	--	--	--

[1] gel formation within 10 minutes of addition of the antimicrobial agent evidences premature polymerization of the cyanoacrylate. In such cases, the antimicrobial agent initiates polymerization.

[2] the mixture is readily resuspended with mild agitation. No gel formed over an 8 week period when stored at room temperature.

The above data demonstrates that of the antimicrobial agents tested, only polyvinylpyrrolidone iodine complex was compatible with the cyanoacrylate composition and, of the polyvinylpyrrolidone iodine complexes tested, only the solid form was compatible. Evidently, the solvent in the solution form of polyvinylpyrrolidone iodine complex initiated polymerization of the cyanoacrylate. Significantly, the suspension formed by the addition of solid polyvinylpyrrolidone iodine complex was curable *in situ* on human skin resulting in a flexible and durable polymeric film.

In addition to the above, tetracycline hydrochloride and hexachlorophene at 5 weight percent based on the total weight of the composition did not result in immediate polymerization of the cyanoacrylate composition but, rather, the

composition polymerized over about a 48 hour period. Accordingly, when mixed immediately prior to use in the manner of this invention, these antimicrobial agents are compatible with the cyanoacrylate composition.

EXAMPLE 2

The following example was conducted to ascertain the antimicrobial effect of a cyanoacrylate polymer film comprising PVP-iodine.

A. Preparation of the Inoculum

Specifically, the surfaces of two TSA plates, 100 x 15 mm, were inoculated with stock cultures (maintained on TSA slants) with the following microorganisms using a sterile inoculating loop: *Staphylococcus aureus* (ATCC No. 6538) and *Staphylococcus epidermidis* (ATCC No. 12228). The plates were incubated at 30° to 35°C for 24 hours. The surfaces of two SAB-DEX agar plates were streaked with *Candida albicans* and incubated at 20-25°C for 48 hours.

The cultures were harvested with sterile saline. Each culture suspension was collected in a sterile container and sufficient sterile saline was added to reduce the microbial count to obtain a working suspension of approximately 1×10^8 CFU's per ml.

The specific microorganisms recited above were selected for inclusion herein because they are common human skin pathogens (bacteria and fungus).

B. Inoculation of Plates

Each of the three test microorganisms was used to inoculate individual TSA plates by streaking them with sterile cotton tip applicators saturated with the appropriate suspension. The plates were allowed to dry.

C. Inhibition Study

Films of polymerized *n*-butyl cyanoacrylate comprising 0%, 10%, 15%, 20% or 30% iodine polyvinylpyrrolidone complex were formed on 25 mm glass fiber filter disks by addition of the corresponding prepolymerized cyanoacrylate composition to the disks and subsequent polymerization *in situ*. The films were then cut into approximately 11 to 13 mm^2 pieces. The pieces were placed in the center of the appropriate inoculated TSA plates. An untreated filter disk was cut into half, and one-half was placed in the center of the appropriate inoculated TSA plate and the other one-half was place in the center of non-inoculated TSA plates, to serve as a negative control. Two inoculated plates of each microorganism were also used as positive controls without the test article. These plates were then incubated for 3 days at 30° to 35°C. After incubation, the plates were removed and examined for any signs of microbial growth inhibition.

The results of this analysis are set forth in Tables I-III below. The sample sizes reported are the portion of the sample actually in contact with the agar. The sizes of the zone of inhibition include the diameters of the entire zone including the test article size.

TABLE I

Results for *Staphylococcus aureus*

SAMPLE: *n*-butyl cyanoacrylate comprising	SAMPLE SIZE[1] (in mm)	ZONE OF INHIBITION[1] (in mm)
0% PVP-I_2	12	12
10% PVP-I_2	12	15
15% PVP-I_2	12.5	14
20% PVP-I_2	11.5	15.5
30% PVP-I_2	12.5	20

SAMPLE: *n*-butyl cyanoacrylate comprising	SAMPLE SIZE[1] (in mm)	ZONE OF INHIBITION[1] (in mm)
Untreated Filter Disk	13[2]	13[2]
Negative Control	13[2]	13[2]
Positive Control	n/a	0

TABLE II

Results for *Staphylococcus epidermis*

SAMPLE: *n*-butyl cyanoacrylate comprising	SAMPLE SIZE[1] (in mm)	ZONE OF INHIBITION[1] (in mm)
0% PVP-I_2	12	12
10% PVP-I_2	12.5	15
15% PVP-I_2	13	15.5
20% PVP-I_2	12.5	20.5
10% PVP-I_2	13	27.5
Untreated Filter Disk	13[2]	13[2]
Negative Control	13[2]	13[2]
Positive Control	n/a	0

TABLE III

Results for *Candida albicans*

SAMPLE: *n*-butyl cyanoacrylate comprising	SAMPLE SIZE[1] (in mm)	ZONE OF INHIBITION[1] (in mm)
0% PVP-I_2	12	12
10% PVP-I_2	12.5	18.5
15% PVP-I_2	12.5	23

SAMPLE: *n*-butyl cyanoacrylate comprising	SAMPLE SIZE[1] (in mm)	ZONE OF INHIBITION[1] (in mm)
20% PVP-I_2	12.5	20.5
30% PVP-I_2	13	29.5
Untreated Filter Disk	13[2]	13[2]
Negative Control	13[2]	13[2]
Positive Control	n/a	0

[1] average of two runs

[2] single run only

The above data demonstrates that the compositions of this invention produce a polymeric cyanoacrylate film which have antimicrobial activity. Based on these results, it is expected that these compositions would be antimicrobial when formed *in situ* on mammalian skin surfaces.

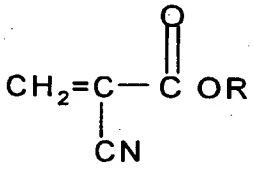
WHAT IS CLAIMED IS:

1. A kit of parts which comprises:

(a) a first container comprising therein a polymerizable cyanoacrylate ester; and

(b) a second container comprising therein an antimicrobially effective amount of a compatible antimicrobial agent.

2. The antimicrobial cyanoacrylate composition according to Claim 1 wherein the polymerizable cyanoacrylate ester is a polymerizable monomer or oligomer of a cyanoacrylate ester which, in monomeric form, is represented by formula I:



I

wherein R is selected from the group consisting of:

alkyl of 1 to 10 carbon atoms,

alkenyl of 2 to 10 carbon atoms,

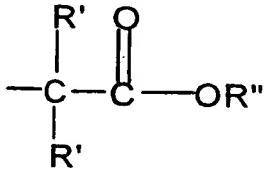
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of the formula:



I

wherein each R′ is independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

3. The kit according to Claim 2 wherein R is alkyl of from 4 to 10 carbon atoms.

4. The kit according to Claim 3 wherein R is alkyl of from 4 to 8 carbon atoms.

5. The kit according to Claim 3 wherein R is selected from the group consisting of butyl, pentyl, octyl, decyl or mixtures thereof.

6. The kit according to Claim 1 wherein said antimicrobial agent is selected from the group consisting of PVP-I_2, hexachlorophene and tetracycline hydrochloride.

1 7. The kit according to Claim 1 which further comprises a biocompatible plasticizer.

8. The kit according to Claim 1 which further comprises a polymerization inhibitor.

1 9. A kit of parts according to Claim 1 further comprising an applicator means for applying the composition onto mammalian skin.

1 10. A kit of parts according to Claim 9 wherein one of the containers and applicator means are combined into a single article.

1 11. A kit of parts according to Claim 9 wherein the containers and applicator means are separate articles.

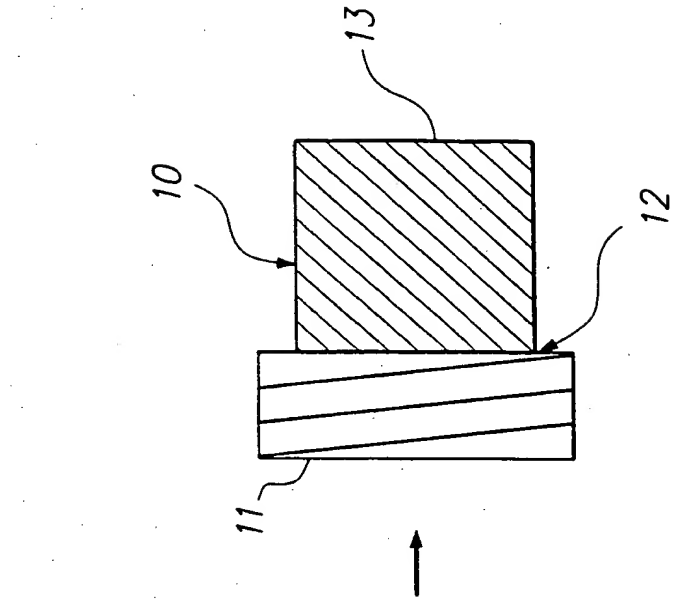


FIG. 1B

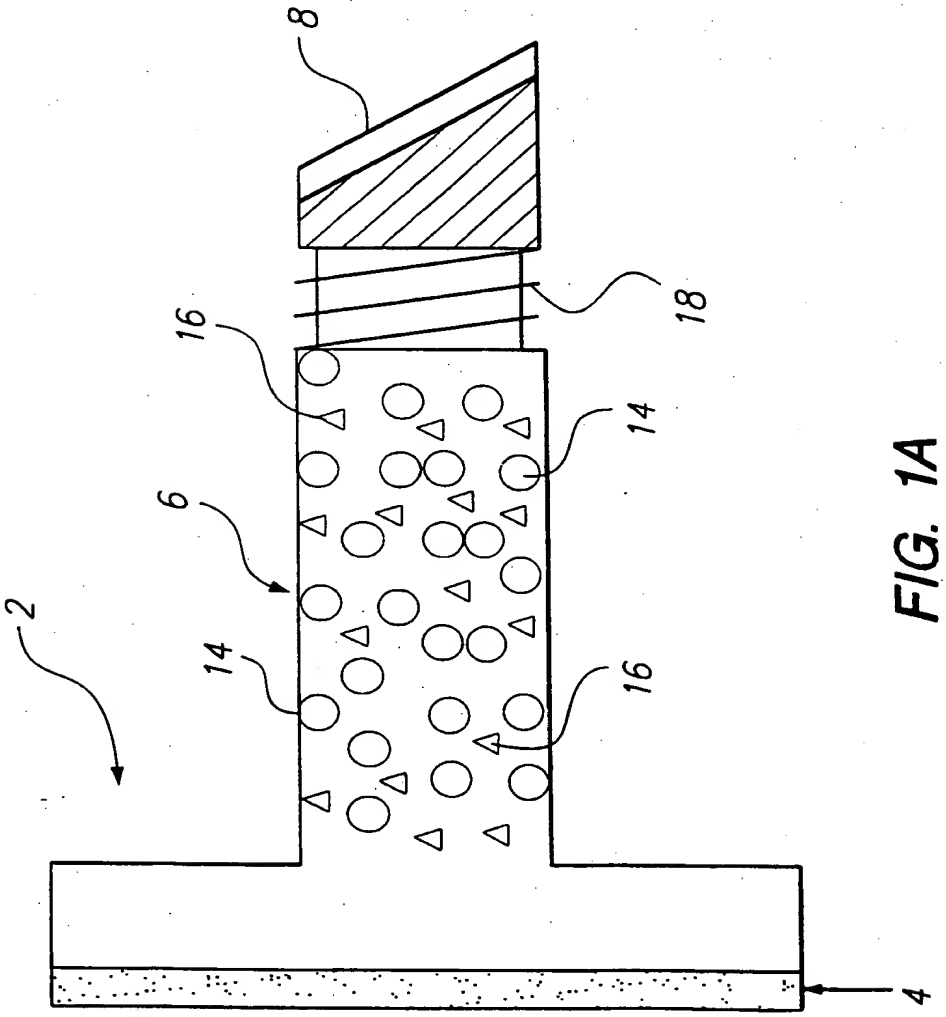


FIG. 1A

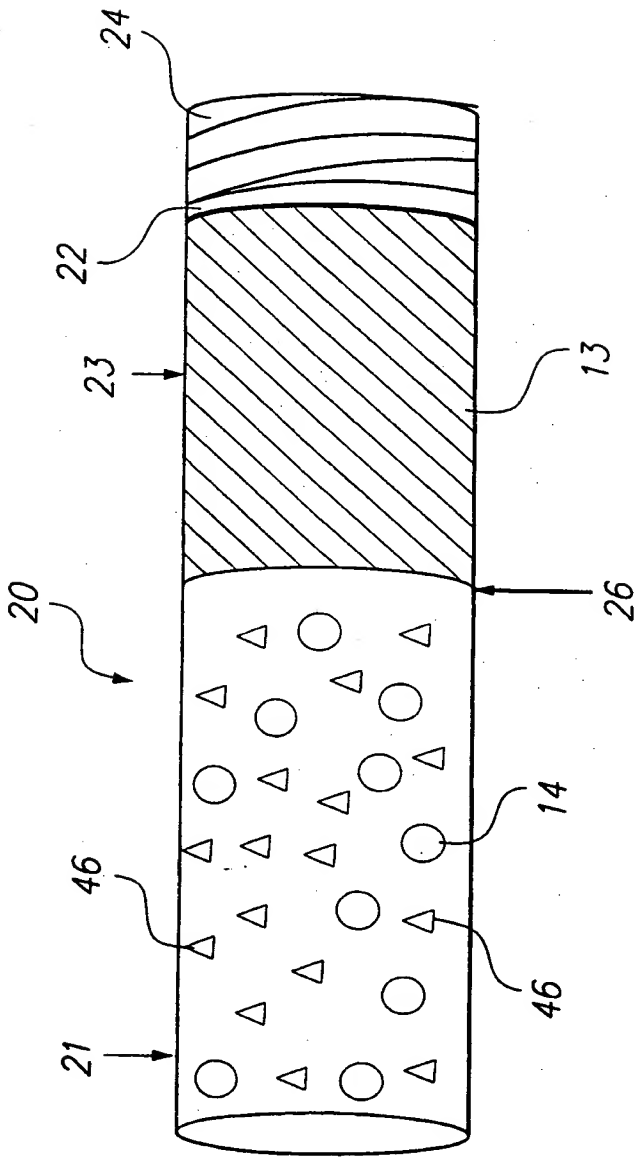


FIG. 2A

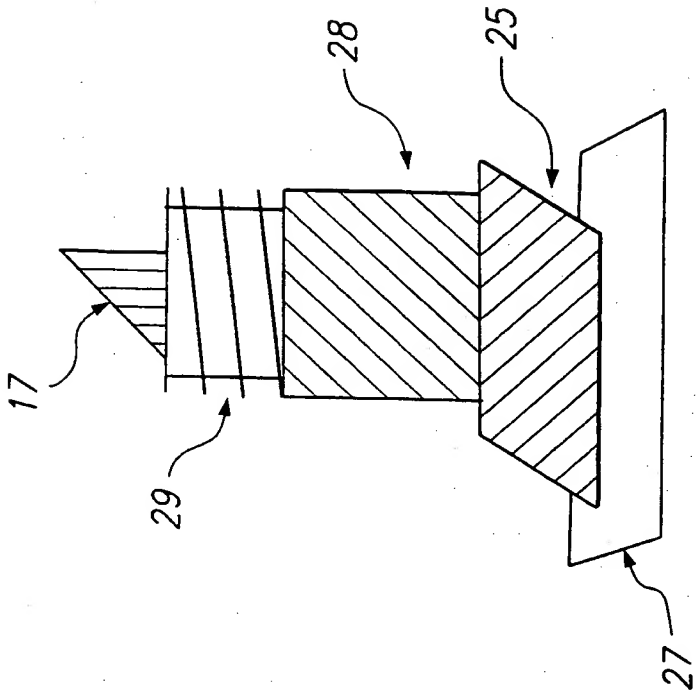


FIG. 2B

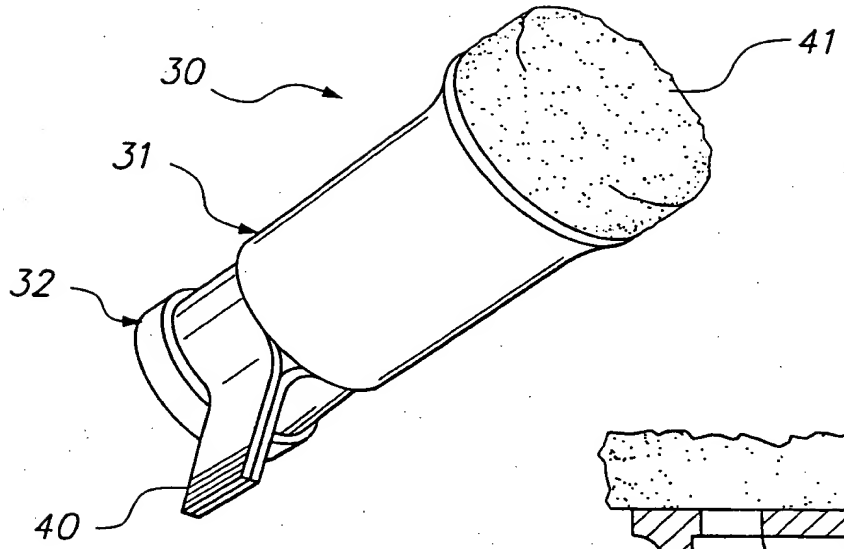


FIG. 3A

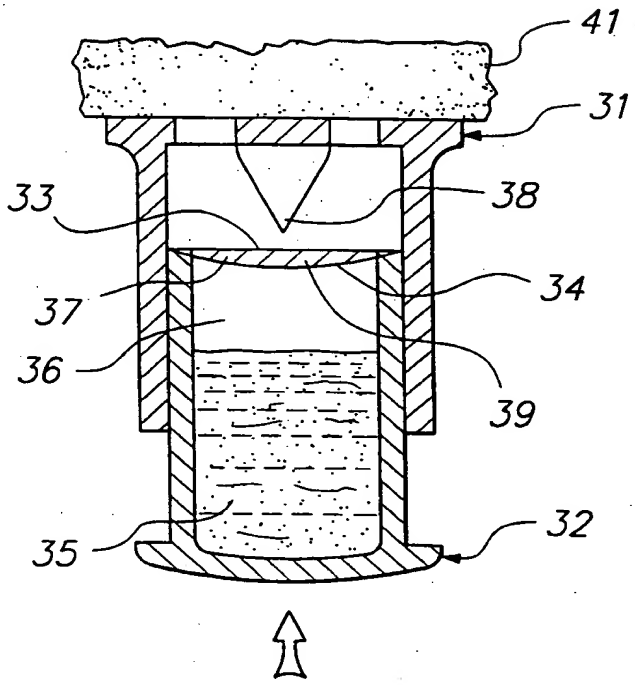


FIG. 3B

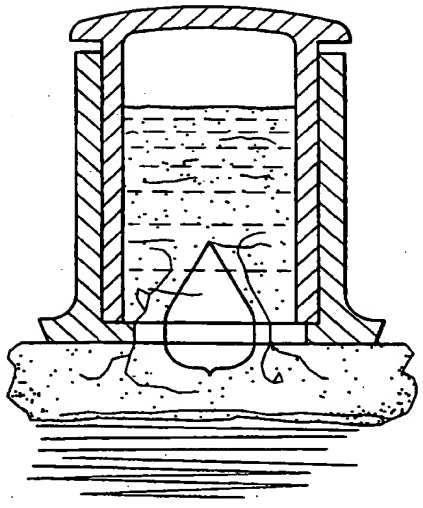


FIG. 3C

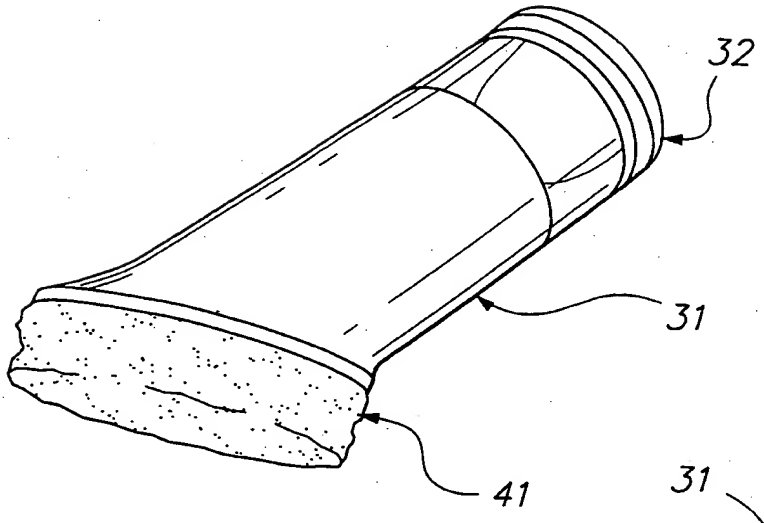


FIG. 4A

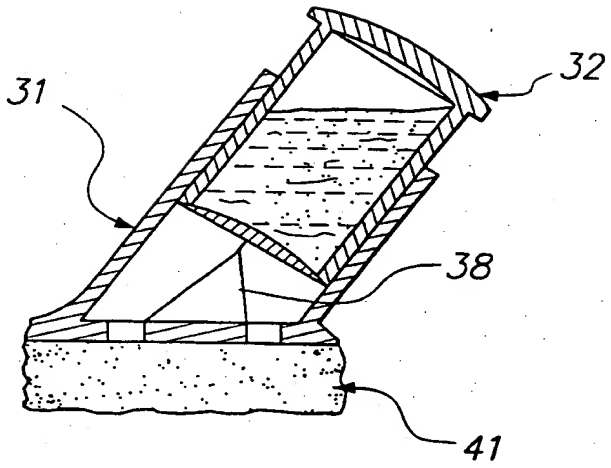


FIG. 4B

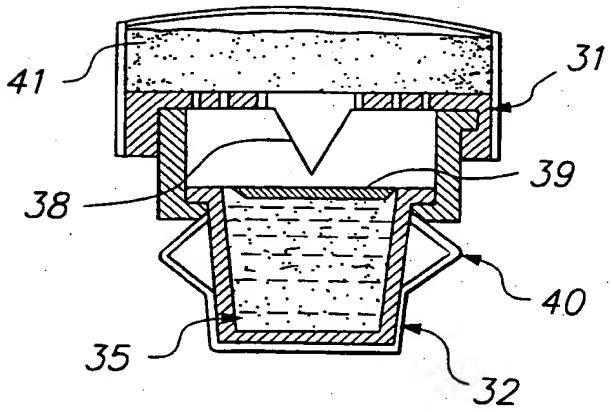


FIG. 5A

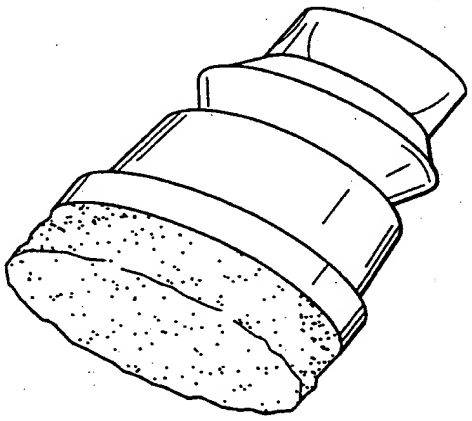


FIG. 5B

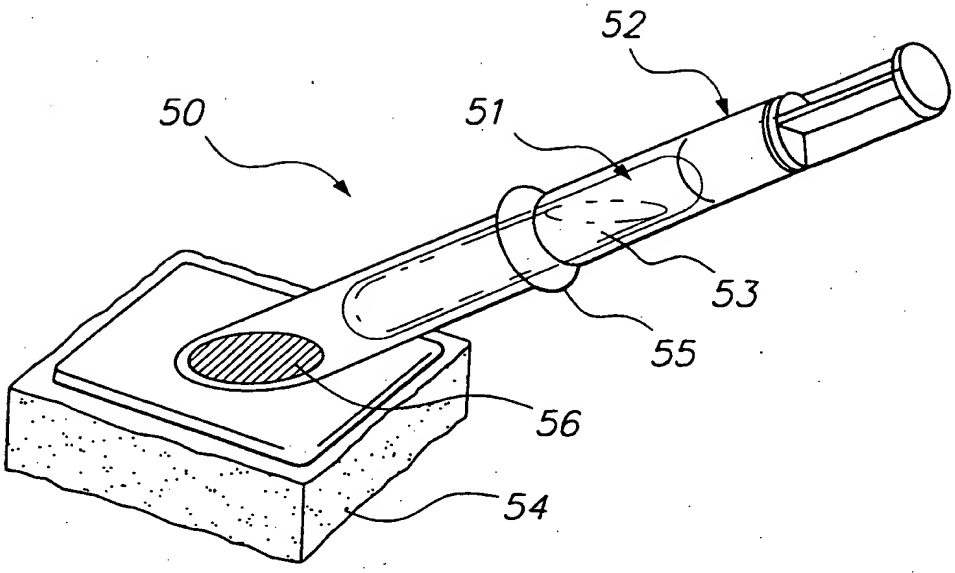


FIG. 6A

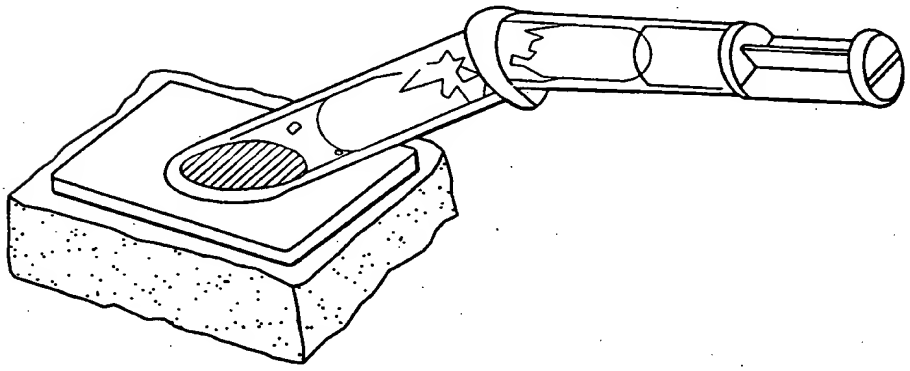


FIG. 6B

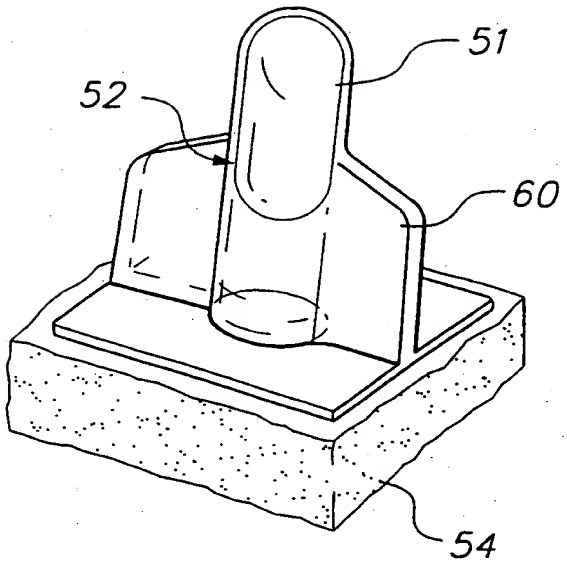


FIG. 7A

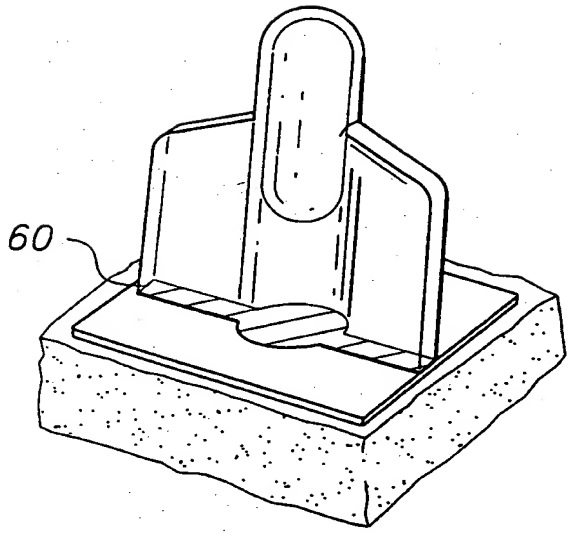


FIG. 7B

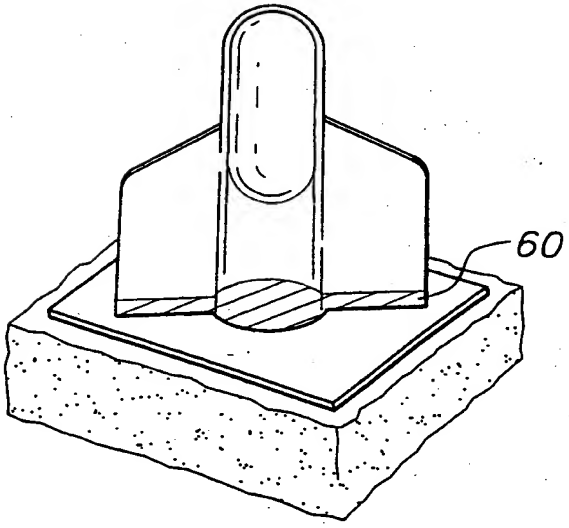


FIG. 7C

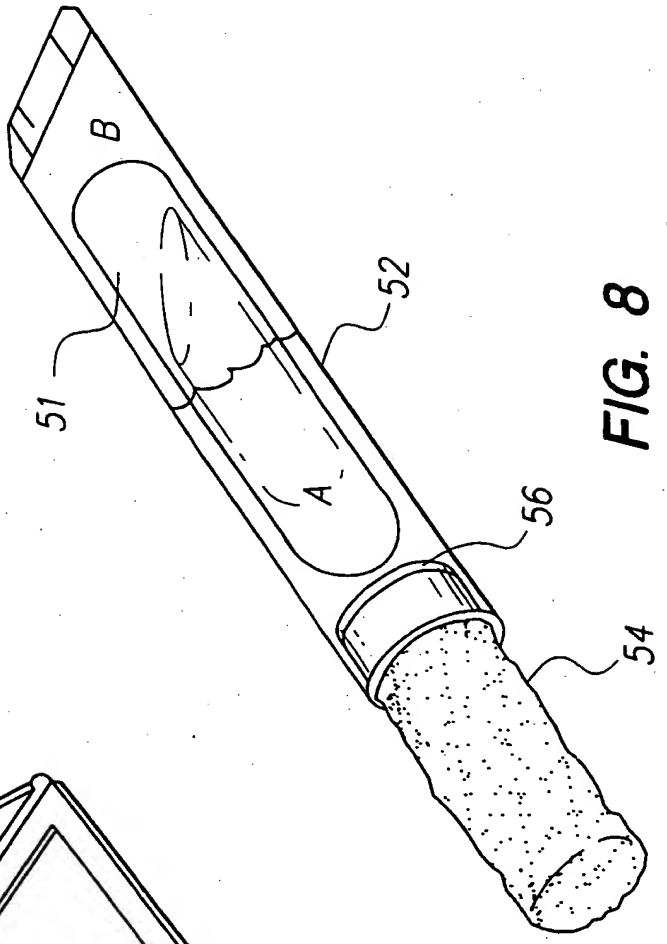


FIG. 8

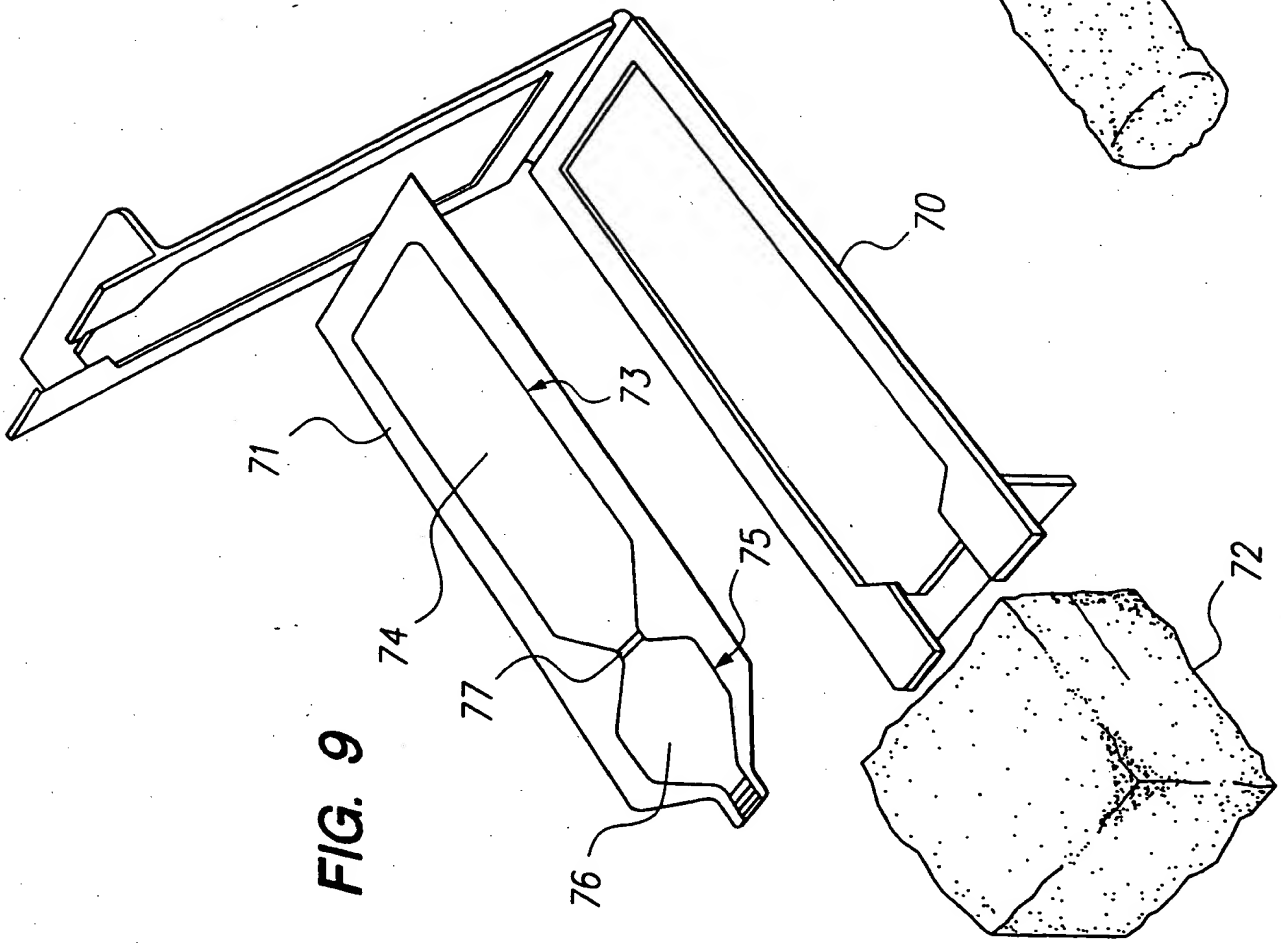


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23380

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B65D 69/00
US CL :206/568, 570 604/46, 87
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/46, 87, 89, 310, 311

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,684,042 A (GREFF ET AL.) 04 November 1997, see entire document.	1-11
Y	US 5,529,577 A (HAMMERSLAG) 25 June 1996, see claims.	1-11
Y	US 5,259,835 A (CLARK ET AL.) 09 November 1993, see figures.	1-11
Y	US 4,808,184 A (TEPIC) 28 February 1989, see columns 2, 3, figures.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
07 JANUARY 1999

Date of mailing of the international search report
01 FEB 1999

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Form PCT/ISA/210 (second sheet)(July 1992)★